REMARKS

Claims 73-81 and 83-93 remain pending in this application. Claims 1-72 and 82 are cancelled with out prejudice. Claims 73-79 are withdrawn. Claims 80, 81, and 83-93 have been rejected.

In the Specification

With respect to the instant specification at page 8, last paragraph, applicants have amended the paragraph to specifically recite "a carbohydrate (CHO) titer greater than 200,000 exhibit greater than 80% killing in the bactericidal assay" (emphasis added). As the first sentence of this paragraph clearly indicates that Figure 7 illustrates bactericidal assays, one skilled in the art would understand that "bacterial assay" is a typographical error and should read - -bactericidal assay- -. Therefore, no new matter has been added by amendment of this paragraph. Furthermore, the instant specification at pages 23-24 and 27 of Example 1, enables the skilled artisan to perform a bactericidal assay and the reagents and steps to be used in this assay.

Claim Rejections – 35 U.S.C. §112, first paragraph

13. Claims 80, 81, and 83-93 stand rejected under 35 U.S.C. §112, first paragraph as being non-enabled with regard to the scope. The Examiner contends that the specification has to necessarily show *in vivo* protective ability of the conjugate vaccine in a mammal, or *in vitro* assay results that correlate with *in vivo* protective efficacy of the conjugate vaccine. Applicants respectfully disagree with this §112, first paragraph rejection.

Applicants respectfully disagree with the Examiner's contention that there is neither any showing, nor predictability that the skilled artisan could reproducibly and successfully practice the claimed method using the Formula I polysaccharide-protein conjugate with or without adjuvant. Example 1 and Figure 7 demonstrate how one skilled in the art would perform bactericidal assays with human sera. From the instant specification and an understanding of the art, the skilled artisan would be knowledgeable in performing bactericidal assays with sera from

humans immunized with the Formula I polysaccharide- protein conjugate of the claimed invention. Furthermore, antibody titers and bactericidal or protective activity have been demonstrated to be related by the "capping phenomenon" described in the instant specification at page 15, lines 11-31. Finally, human and rabbit data, although correlative, do not necessarily have the exact same geometric mean titers. For example, Figure 7 shows the results of human sera and Table IV (Example 7) represents rabbit data, both of which demonstrate high titers. Applicants emphasize that subjects immunized with the GASP- protein conjugates result in sera with high titers to GASP-CHO (Example 7 and Table IV). For these reasons and those described in further detail below, applicants believe that the instant application as filed is enabled for methods of eliciting protective antibodies using the Formula I polysaccharide- protein conjugate.

Applicants' specification enables a method of eliciting protective antibodies specific to group A streptococcal (GAS) polysaccharides. In particular, the antibodies specific to GASP of Example 1, may be shown to be protective through a series of four types of experiments: (i) bactericidal assays; (ii) relationship between anti-CHO titers and opsonophagocytosis by human sera; (iii) studies of phagocytosis by human sera; and (iv) absorption assays. An absorption assay that removes GASP-specific antibodies in sera also indicates that GASP-specific antibodies are protective by causing the sera to lose opsonophagocytic ability. GASP-specific antibodies are specific to the GAS polysaccharide component of the conjugate in the claimed methods of eliciting protective antibodies; therefore, antibodies elicited by the conjugate are protective.

The four experiments as described in Example 1 at pages 24-28 of the instant specification, provide sufficient details to enable one skilled in the art to perform such assays to support the claimed invention. The specification discloses antibodies to the group A carbohydrate antigen that are readily detected in human sera and that the titer of these antibodies is age dependent (*See*, page 10, lines 7-12). Furthermore, the specification discloses that these naturally occurring antibodies produce a bactericidal effect resulting from their opsonphagocytic activity (*See*, page 10, lines 17-22). See also Figure 4 of Example 1

which discloses that the group A carbohydrate antibodies present in human sera are phagocytic and therefore bactericidal against group A Streptococcal bacteria (page 24, lines 1-28). The instant specification coupled with knowledge in the art provide considerable direction and guidance and undue experimentation would not be necessary for one skilled in the art to obtain the protective antibodies used in the claimed invention. In contrast to the Examiner's contention that ELISA antibody titers are not reflective of the bactericidal or protective activity of an antiserum or antibody, applicants respectfully direct the Examiner's attention to pages 16-17 where the commonly known "capping" phenomena is believed to be associated with GASP-liposome conjugates and an increase in antibody titers.

Example 7, Table IV shows the GASP-specific antibody titers (geometric mean) of five rabbits vaccinated with either GASP or conjugated GASP. The ELISA titers elicited by the GASP-aluminum hydroxide conjugate at day 52 ranged from 76,700 to 287,500. This rabbit data may be used as a guide for corresponding human data in conjunction with the results of Figure 7 which represents a CHO titer greater than 200,000 for individual human sera.

Applicants also present the Declaration of Francis J. Michon under 37 C.F.R. §1.132 reporting data from an article presented at the Lancefield International Symposium on Streptococci and Streptococcal Disease [Sabharwal, et al. presented at the Proceedings of the XIV Lancefield International Symposium on Streptococci and Streptococcal Disease, Auckland, New Zealand, 1999. October 11-15. (in press)]. The article is co-authored by Hemant Sabharwal, Milan S. Blake, John B. Zabriskie, and Francis Michon. Milan S. Blake, John B. Zabriskie, and Francis Michon are co-inventors of the instant application. The Sabharwal, et al. publication reports of the *in vivo* protective effects in Balb/c mice immunized with Group A streptococcal carbohydrates conjugated to tetanus toxoid against three types of group A Streptococcus (types 3, 6, and 14). Paragraphs 8-12 of the Declaration of Francis J. Michon, and specifically Tables 1 and 2, show that the Group A streptococcal antibodies passively protect against an *in vivo* mouse challenge model. Paragraph 10 and specifically Tables 3 and 4 show that active immunization with Group A streptococcal carbohydrates conjugated to tetanus toxoid protects mice against two types of live streptococci. Dr. Michon indicates in paragraph 13 of his Declaration that the skilled artisan would be capable of successfully practicing the claimed

method without undue experimentation from the present specification as demonstrated by the work in the Sabharwal, et al. publication. The Declaration enclosed herewith and the Sabharwal, et al. publication provide further support that the methods described in the instant application are enabled and that one skilled in the art is capable of reproducing and successfully using the claimed methods.

Thus, in view of the above-mentioned arguments, as supported by the results of the article, one skilled in the art would be enabled to perform the bactericidal assays as described in the instant specification, as well as, the methods of eliciting protective antibodies as claimed. Applicants respectfully request reconsideration and withdrawal of this §112, first paragraph rejection.

Prior Art

14. The prior art made of record and not currently relied upon in any of the rejections is considered by the Examiner to be pertinent to applicants' disclosure for allegedly teaching that ELISA assays are not reliable indicators of protection against capsulated bacterial pathogens. Applicants point out that Christodoulides and Heckels use such ELISA assays and they further suggest "the importance of relevant biological assays such as bactericidal killing" (pg. 2958, left column). The instant specification describes ELISA assays together with bactericidal assays, where in Figure 4, there is a significant inhibition of growth of nine colony forming units of group A-type 6 Streptococci with human serum having a high ELISA titer reactive to the group A carbohydrate in a rotated tube. In addition, applicants provide the Declaration enclosed herewith and the Sabharwal, et al. publication co-authored by the inventors of the instant application [Sabharwal, et al. presented at the Proceedings of the XIV Lancefield International Symposium on Streptococci and Streptococcal Disease, Auckland, New Zealand, 1999. October 11-15. (in press)] which reports of conjugated Group A streptococcal antibodies that are passively protective against an *in vivo* mouse model and that active immunization with Group A streptococcal CHO conjugated to tetanus toxoid protects mice challenged with live Streptococci. Therefore, although the article by Christodoulides and Heckels may suggest that the ELISA assays are not reliable indicators of protection alone, the series of assays (i.e., bactericidal assays,

assays determining the relationship between anti-CHO titers and opsonophagocytosis by human sera, studies of phagocytosis by human sera, and absorption assays) that are described in the instant specification support the claimed methods of eliciting protective antibodies. Thus, in view of the above arguments and the enclosed Declaration by Francis Michon containing Group A streptococcal conjugate data, reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for the timely consideration of this amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2016-4005US1.

Respectfully submitted,

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By: _____

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